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Palladium-Catalyzed Direct Intermolecular α-Arylation of Amides with Aryl Chlorides

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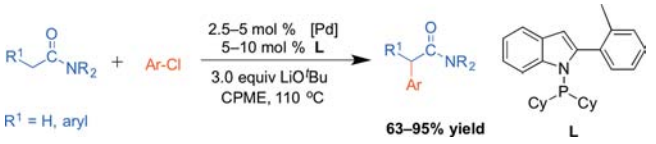
ABSTRACT



An efficient catalytic system for the direct intermolecular α-arylation of acetamide derivatives with aryl chlorides is presented. Chemoselectivities up to 10:1 in the mono- and diarylation of acetamides were achieved by careful selection of bases, solvents, and stoichiometry. Bis-arylated amides were prepared in up to 95% yield.

Amides are ubiquitous building blocks for fine chemicals[1] and pharmaceuticals[2] and are common subunits in natural products.[3] The direct cross-coupling of unfunctionalized amides with aryl bromides to form C−C bonds is a synthetically efficient and straightforward approach to their elaboration[4] and has generated considerable interest.[5]

In pioneering studies on the arylation of amides, the Hartwig group described a (BINAP)Pd-based catalyst for the α-arylation of acetamides with aryl bromides (Scheme 1A). Yields up to 72% were obtained despite competing formation of diarylated byproducts.[5c] They also demonstrated that the mechanism of oxidative addition of aryl chlorides proceeded through a palladium species bearing a single monodentate phosphine in the intramolecular α-arylation of amides to produce oxindoles.[6] Palladium catalysts ligated with bidentate ligands will activate aryl chlorides at temperatures around 100 °C.[7] Hartwig and co-workers later developed a general procedure for amide α-arylation by α-deprotonation, transmetalation to zinc, and cross-coupling with aryl bromides (Scheme 1B).[5a] Contrary to the successful application of aryl bromides to amide α-arylation, *the intermolecular α-arylation of amides with aryl chlorides* is unknown to our knowledge. Aryl chlorides are generally less reactive than aryl bromides in oxidative additions.[8] Nonetheless, aryl chlorides are less expensive and more readily accessible than aryl

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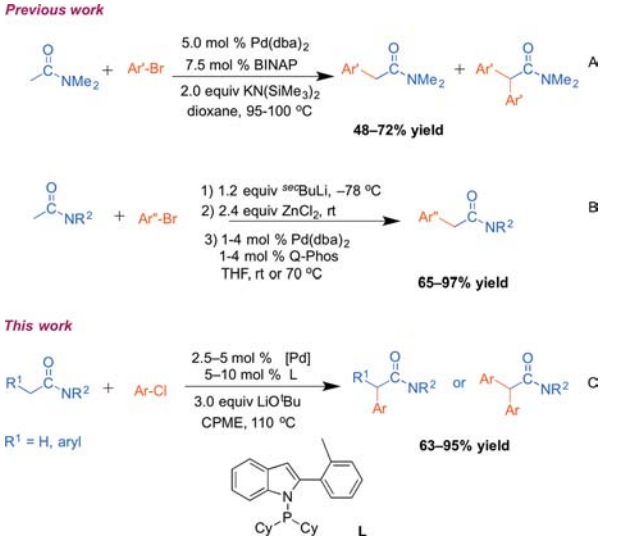
bromides, making their use in cross-coupling reactions highly desirable.

We have been interested in the catalytic functionalization of weakly acidic sp^3-hybridized C−H bonds[9] (pK_a's 28−35 in DMSO) and have recently developed methods for the *in situ* deprotonation and coupling of diarylmethanes,[10] sulfones,[11] sulfoxides,[12] and chromium-activated benzylic amines.[9]

Based on these advances, we hypothesized that a palladium-catalyzed deprotonative cross-coupling process (DCCP) for the arylation of amides (pK_a > 35) with aryl chlorides should be possible (Scheme 1C). Herein we report the first chemoselective mono- and bis-arylation of *N,N*-dialkyl acetamide derivatives with aryl chlorides. The palladium catalyst identified for this challenging reaction is based on Kwong's indole phosphine[13] and alkoxide bases.

Scheme 1. Palladium-Catalyzed α-Arylation of Amides



We initiated studies of the α-arylation of amides with aryl chlorides employing the same catalyst and conditions we developed for the palladium-catalyzed arylation of sulfones with aryl bromides[11] ($PhSO_2CH_3$, pK_a 29).[14] Under these conditions, however, only a 25% yield of the monoarylated amide **3aa** was obtained (Table 1, entry 1). Based on our previous experience with the arylation of sulfoxides with aryl chlorides,[12] we hypothesized that catalyst activation might be problematic. We, therefore, turned to the Buchwald-type precatalysts (Figure 1), which readily form active catalysts.[15,16] As shown in Table 1, four common solvents [toluene, cyclopentyl methyl ether (CPME), dioxane, and dimethoxyethane (DME)] were screened using the second generation palladium dimer **L1**[15,16] with Kwong's indole-based phosphine (**L**; see Scheme 1C). CPME was determined to be the most effective solvent, providing a mixture of the mono- and bis-arylated products in a 5:1 ratio (entries 2−5, Table 1). From these reactions, the monoarylated **3aa** was isolated in up to 63% yield (Table 1, entry 3). The other solvents (toluene, dioxane, and DME) led to generation of **3aa** in lower yields (15−59%) and with inferior ratios of mono- to bis-arylated products (Table 1, entry 3 vs 2, 4, and 5). Further screening of six bases [LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$] resulted in yields from 6−63% of monoarylated **3aa** and 2:1 to 5:1 ratios of monoarylated **3aa** to bis-arylated **4aa** (Table 1, entries 3 and 6−10). To improve the yield and selectivity for **3aa**, Buchwald's third generation palladium dimer **L2**[17] and the third generation indole-based precatalyst **L3**[17] (Figure 1) were investigated with chlorobenzene **1a** and *N,N*-diethylacetamide **2a**. Unfortunately, the ratio of monoarylation **3aa** to bis-arylation **4aa** dropped below 3:1 (Table 1, entries 11 and 12). Our best conditions for monoarylation of acetamides with aryl chlorides were, therefore, 2.5 mol % second generation palladium dimer **L1** and 10 mol % **L** with 3 equiv of LiO^{t}Bu in CPME at 110 °C for 12 h.

With our optimized reaction conditions, we examined the scope of aryl chlorides in the monoarylation with **2a** (Table 2). Phenyl chloride (**1a**) provided a 5:1 ratio of mono-/bis-arylated products from which the monoarylated product **3aa** was isolated in 63% yield (Table 2, entry 1). Likewise, alkyl substituted aryl chlorides, such as 4-*tert*-butyl chlorobenzene (**1b**), 4-chlorotoluene (**1c**), and 3-chlorotoluene (**1d**) coupled with **2a** in moderate to good selectivities (5:1−10:1 mono-/bis-arylated product) in 63−70% yield of the major products (entries 2−4). Aryl chlorides with *ortho*-substitution, such as 2-chlorotoluene and 1-chloronaphthalene, were poor substrates (< 10% yield) in this reaction. This appears to be a limitation of the palladium catalyst with Kwong's indole-based phosphine.

Aryl chlorides bearing electron donating groups, such as 3-chloro-*N,N*-dimethylaniline (**1e**) or 1-chloro-4-methoxybenzene (**1f**), gave the monocoupled products in 70−72% yield with 7:1 to 10:1 selectivity (entries 5−6). Lower selectivities (3:1−5:1), however, were observed when

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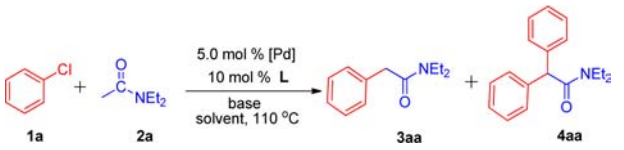
Table 1. Optimization of the α-Arylation of *N,N*-Diethylacetamide **2a** with Chlorobenzene **1a**[a]



entry	base	solvent	**3aa** NMR yield (%)	**4aa** NMR yield (%)
1[b]	LiO^{t}Bu	toluene	25	trace
2	LiO^{t}Bu	toluene	59	14
3	LiO^{t}Bu	CPME	63[c]	12
4	LiO^{t}Bu	dioxane	34	14
5	LiO^{t}Bu	DME	15	3
6	NaO^{t}Bu	CPME	45	20
7	KO^{t}Bu	CPME	50	14
8	LiN(SiMe$_3$)$_2$	CPME	12	trace
9	NaN(SiMe$_3$)$_2$	CPME	15	trace
10	KN(SiMe$_3$)$_2$	CPME	6	trace
11[d]	LiO^{t}Bu	CPME	36	14
12[e]	LiO^{t}Bu	CPME	29	15

[a] Reactions performed using 1.0 equiv of **1a**, 2.0 equiv of **2a**, and 3.0 equiv of base on a 0.2 mmol scale. [b] 20 mol % **L** used. [c] Isolated yield. [d] 2.5 mol % **L2** and 10 mol % **L** used. [e] 5.0 mol % **L3** used.

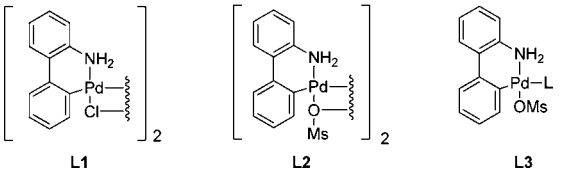
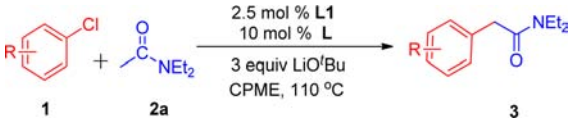


Figure 1. Buchwald's second and third generation dimeric precatalysts and the third generation precatalyst bound to Kwong's indole-based phosphine (**L**).

aryl chlorides bearing electron-withdrawing substituents, such as 1-chloro-4-fluorobenzene (**1g**) and 1-chloro-3-(trifluoromethyl)benzene (**1h**, entries 7−8). The higher percentages of diarylated products could be due to the increased acidity of the monoarylated products. Nonetheless, the yields of these substrates (63−72%) were comparable to others in Table 2. Other sensitive functional groups, such as nitro, cyano, or esters, were incompatible with our reaction conditions.

Our starting point for the optimization of the bis-arylation of acetamides with aryl chlorides was entry 6 of Table 1, where NaO^{t}Bu was employed as the base in CPME and the bis-arylated **4aa** was formed in 20% yield. We found that the third generation indole phophine-based precatalyst **L3** was the best palladium source in terms of yield (84%) in combination with CPME (Table 3, entry 1 vs entries 3 and 5). In general, NaO^{t}Bu was more effective than KO^{t}Bu with different palladium sources (entries 1, 3, 5 vs 2, 4 and 6), so it was employed in the bis-arylation of **2a** with aryl chlorides.

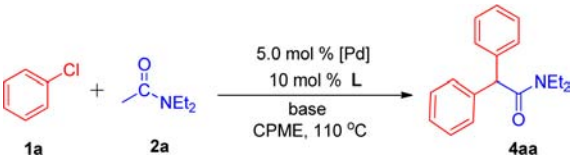
Table 2. Substrate Scope of Aryl Chlorides in the α-Arylation of **2a** to Give **3**[a]



entry	Ar−Cl	product	ratio[b]	isolated yield (%)
1	Ph−Cl	**3aa**	5:1	63
2	4-^{t}Bu−C$_6$H$_4$−Cl	**3ab**	10:1	68
3	4-Me−C$_6$H$_4$−Cl	**3ac**	5:1	63
4	3-Me−C$_6$H$_4$−Cl	**3ad**	7:1	70
5	3-Me$_2$N−C$_6$H$_4$−Cl	**3ae**	7:1	72
6	4-CH$_3$O−C$_6$H$_4$−Cl	**3af**	10:1	70
7	4-F−C$_6$H$_4$−Cl	**3ag**	3:1	65
8	3-CF$_3$−C$_6$H$_4$−Cl	**3ah**	5:1	72

[a] Reactions performed using 1.0 equiv of **1**, 2.0 equiv of **2a** on 0.2 mmol scale. [b] Ratio is between mono- and bis-arylated product.

Table 3. Optimization of the Diarylation of *N,N*-Diethylacetamide **2a** with **1a**[a]



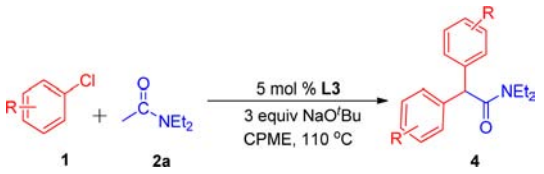
entry	[Pd]	base	NMR yield (%)
1[b]	**L3**	NaO^{t}Bu	84
2[b]	**L3**	KO^{t}Bu	69
3	**L2**	NaO^{t}Bu	69
4	**L2**	KO^{t}Bu	50
5	**L1**	NaO^{t}Bu	64
6	**L1**	KO^{t}Bu	56

[a] Reactions performed using 2.0 equiv of **1a**, 1.0 equiv of **2a** on a 0.2 mmol scale. [b] 0 mol % additional **L** used.

Under the optimized conditions of entry 1 in Table 3, the diarylation of *N,N*-diethylacetamide **2a** with a variety of aryl chlorides and 5 mol % third generation indole-based precatalyst was investigated. As shown in Table 4, 70%−80% isolated yields were achieved in the diarylation. Chlorobenzene (**1a**), 4-*tert*-butyl chlorobenzene (**1b**), and 3-chlorotoluene (**1d**) furnished products **4aa**, **4bb**, and **4dd** in 80%, 76%, and 70% yields, respectively. Electron-rich 4-chloroanisole (**1f**) afforded the double-coupled product **4ff** in 72% yield. Electron-deficient 1-chloro-4-fluorobenzene (**1g**) underwent coupling in 72% yield to provide **4gg**.

Encouraged by the results of the diarylation with aryl chlorides, we next examined the arylation of arylacetamides

Table 4. Substrate Scope of Aryl Chlorides in the Diarylation of **2a**[a]

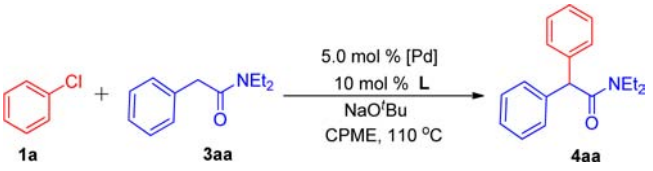


entry	Ar–Cl	product	isolated yield (%)
1	Ph–Cl	**4aa**	80
2	4-^{t}Bu–C_6H_4–Cl	**4bb**	76
3	3-Me–C_6H_4–Cl	**4dd**	70
4	4-MeO–C_6H_4–Cl	**4ff**	72
5	4-F–C_6H_4–Cl	**4gg**	72

[a] Reactions performed using 2.0 equiv of **1**, 1.0 equiv of **2a** on a 0.2 mmol scale.

to yield diarylated products **4** bearing two different aryl groups. As summarized in Table 5, a short survey of Buchwald-type precatalysts led to the choice of the third generation indole-based precatalyst **L3**, which generated 95% yield of the product **4aa** when 1.5 equiv of chlorobenzene was employed (Table 5, entry 1). Decreasing the loading of precatalyst from 5.0 to 2.5 mol % also led to a satisfactory yield (91%, entry 2). The second and third generation palladium dimers were also examined in the arylation of **3aa** with chlorobenzene, but gave lower yields (Table 5, entries 3 and 4).

Table 5. Optimization of the Arylation of **3aa** with **1a**[a]

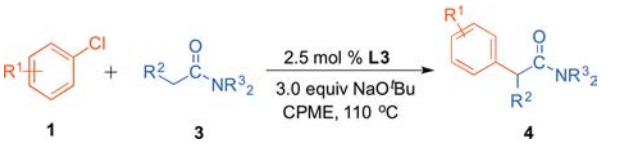


entry	[Pd]	catalyst/ mol %	NMR yield (%)
1[b]	**L3**	5	95
2[b]	**L3**	2.5	91
3	**L2**	2.5	85
4	**L1**	2.5	76

[a] Reactions performed using 1.5 equiv of **1a**, 1.0 equiv of **3aa** on a 0.2 mmol scale. [b] 0 mol % **L** used.

Our optimal conditions employed NaO^{t}Bu as a base in CPME with 2.5 mol % of the indole-based precatalyst **L3** at 110 °C. Under these conditions, various aryl chlorides were examined (Table 6). The alkyl substituted 4-*tert*-butyl chlorobenzene (**1b**) and 3-chlorotoluene (**1d**) gave diarylacetamides **4ab** and **4ad** in 95% and 93% yield, respectively. 3-Chloro-*N*,*N*-dimethylaniline (**1e**) reacted smoothy to give the product **4ae** in 90% yield.

Table 6. Substrate Scope of Aryl Chlorides in the α-Arylation of Arylacetamides **3**[a]



entry	R^1	R^2	R^3	isolated yield (%)
1	H	Ph	Et	90
2	4-^{t}Bu	Ph	Et	95
3	3-Me	Ph	Et	93
4	3-Me_2N	Ph	Et	90
5	4-MeO	Ph	Et	88
6	4-pyrrol	Ph	Et	91
7	4-F	Ph	Et	90
8	4-^{t}Bu	Ph	pyrrolidine	90
9	4-^{t}Bu	Ph	piperidine	93
10	4-^{t}Bu	3-pyridyl	Et	83
11	4-^{t}Bu	3-thiophenyl	Et	77

[a] Reactions performed using 1.5 equiv of **1**, 1.0 equiv of **3**, and 3.0 equiv of base on a 0.2 mmol scale.

Electron-rich 4-chloroanisole (**1f**) and 4-pyrrole chlorobenzene (**1i**) were successfully coupled with **3aa** to afford **4af** and **4ai** in 88% and 91% yield, respectively. Likewise, 1-chloro-4-fluorobenzene (**1g**) reacted smoothly to give **4ag** in 90% yield.

Changing the substituents on the amide nitrogen of the substrates had little impact on the reactivity in the arylation. Pyrrolidine (**3ba**) and piperidine (**3ca**) acetamide derivatives gave arylation products **4ba** and **4ca** in 90% and 93% yield, respectively (Table 6). Substrates that bear heteroaryl groups on the acetamide, such as 3-pyridyl (**3aj**) and 3-thiophene (**3ak**), were also suitable substrates under the optimized conditions, providing **4aj** and **4ak** in 83% and 77% yield, respectively.

In summary, we report the first deprotonative cross-coupling process for the intermolecular arylation of amides with aryl chlorides. Buchwald-type precatalysts formed with Kowng's indole-based ligand effectively catalyzes the direct α-arylation of acetamides with aryl chlorides. It is noteworthy that the chemoselectivity between mono- and bis-arylated products was effectively controlled by base and solvent combinations.

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Supporting Information Available. Procedures, characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.